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A specific two-pulse release of rivastigmine using a modified time-controlled delivery system: A proof of concept case study

Adel Penhasi[a,b,*], Mila Gomberg[a]

[a] Department of Research and Development, PolyCaps Ltd., Tel Aviv 61580, Israel
[b] Department of Pharmaceutical Engineering, The Azrieli Jerusalem College of Engineering, Jerusalem 91035, Israel

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ABSTRACT

Currently, the orally administrated rivastigmine is based on twice daily formulations which also demand a titration process in order to increase the tolerability of the drug. In the present study an attempt was made to design and prepare an innovative single unit, once daily, double pulse release formulation for oral administration of rivastigmine in order to increase patient compliance without causing tolerance development. The pulsatile system was prepared as a tablet-in-tablet using a compression-coating method. An in-vitro dissolution test was utilized to determine the release profile of the drug from this system. The results showed that the designed delivery system provided two consecutive pulses of rivastigmine with a time difference of 6.5 h between the peaks of the pulses. The outer tablet provided an immediate release which lasted up to 4 h. The inner tablet, on the other hand, which was a film coated tablet, presented a capability of time-controlled delivery which was manifested by a lag time of 3 h followed by a burst release. The lag time was dependent, to a considerable extent, on the film coating weight. Surprisingly, the compression-coating did not alter the release features of the inner tablet whatsoever.

1. Introduction

Dementia is characterized by a severe memory disorder, cognitive disfunction and deterioration of emotional capacities. Alzheimer's disease is the most common cause of dementia [1]. Rivastigmine is indicated for symptomatic treatment of patients with mild to moderately severe Alzheimer's dementia and dementia associated with Parkinson's disease [2,3]. It is a non-competitive, slowly reversible cholinesterase inhibitor, which acts by inhibiting both enzymes: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) which are responsible for the degradation of acetylcholine. Rivastigmine has a central nervous system selectivity over peripheral inhibition. Gastrointestinal symptoms, such as nausea, vomiting and diarrhea, are the most frequently reported adverse events of the treatment with rivastigmine [2–4].

Rivastigmine is rapidly and completely absorbed with absolute bioavailability of about 40% (3 mg dose) and peak plasma concentrations reaching in approximately 1 h. The elimination half-life is about 1.5 h, with most elimination as metabolites via the urine [3].

Since rivastigmine is classified as an intermediate-acting or pseudo-irreversible agent due to its relatively prolonged inhibition of AChE (of up to 10 h) [3,4] a fast release of the drug formulation is far superior to an extended release. Likewise, due to the fact that the drug administration is accompanied by a titration procedure, in order to increase the tolerability of the drug, the likelihood that an extended release may cause the evolvement of drug tolerance, demanding an increasing dose frequency or dose level [5], should not be underestimated.

Currently, rivastigmine is administrated either orally (as a hard gelatin capsule or solution) providing immediate release or by a transdermal patch formulation presenting an extended release profile [6,7]. The hard gelatin capsule is generally administrated with the effective dose of 3–6 mg twice a day [6].

In attempts to minimize the limitations of the currently existing rivastigmine formulations and maximize the efficacy of the drug, many formulations have recently been developed, including the controlled release formulations [8,9] and the formulations for increasing the bioavailability and brain targeted delivery of rivastigmine [10].

A pulsatile drug delivery system (PDDS) is generally a time-controlled delivery system which is able to release a drug in different doses (pulses) rapidly within a relatively short time period (burst release) with a predetermined off-release (break) period between them [11–15]. PDDS is an efficient way for the delivery of a drug which may exhibit biological tolerance which is a decrease in drug's efficacy upon constant

* Corresponding author. Department of Research and Development, PolyCaps Ltd., Atidim Technology Park, Bldg #4, 13th fl., P.O. Box 58143, Tel Aviv 61580, Israel.
E-mail address: adel@polycaps.com (A. Penhasi).

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Fig. 1. A schematic illustration demonstrating the cross-section of the tablet-in-tablet dual system, including the outer tablet (OT) and the inner tablet (IT) which is coated by a time-controlling film coating (FC) consisting of calcium pectinate (CaP) particulates and ethylcellulose (EC) as a rigid film forming polymer.

exposure to the drug. Drug tolerance can especially be developed by using the controlled-release or extended release formulations providing a constant drug release [12].

To date, different oral biphasic (dual) delivery systems including tablet-in-tablet and double layer tablets have been developed and evaluated for creating pulsatile release of different active materials [16–19]. However, so far no delivery system has been specifically developed for a pulsatile release of rivastigmine.

The present study was planned to examine a unique release profile of the drug, from an orally administrated formulation, which is entirely different from those provided by the currently marketed products. The main idea was to design a novel, once daily, two-pulse release formulation in order to minimize the adverse effects of rivastigmine and increase patient compliance.

The formulation was based on an innovative single unit dosage form which consisted of a tablet-in-tablet dual system where an inner coated tablet was surrounded by an outer layer (outer tablet) using a compression-coating process (Fig. 1) [20]. Both the inner and outer tablets each contained 3 mg rivastigmine corresponding to 4.8 mg rivastigmine hydrogen tartrate. The unique matrix composition of the outer tablet was formulated to provide the first release pulse as a semi-slow release (fast sustained release) whereas the inner tablet was designed to release the second pulse of the drug in a burst manner following a predetermined lag time. The latter was composed of a unique fast disintegrating core and a novel film-coating combination, providing a certain lag time which was needed to separate two pulses of the drug. The film-coating structure is based on a unique combination of a hydrophobic, rigid film forming polymer such as ethylcellulose and hydrophilic water insoluble particulates such as calcium pectinate (CaP) which are evenly embedded within the film forming polymer. Upon exposure of the inner tablet to the gastrointestinal liquids or any dissolution medium the aqueous solution enters through the particulates, in a controlled manner, into the core creating an increasing osmotic pressure which is concurrently exerted onto the film coat. At a specific point of time, the inner pressure overcomes the strength of the film coat and breaches it. At the same time the core immediately disintegrates, resulting eventually in a fast release of drug [21].

This study aimed to explore the release profile of rivastigmine from the designed dual delivery system with a focus on the effect of the compression coating process on the lag time between two pulses which is provided by the film-coating combination of the inner tablet. Note that, in general, the lag time is defined as the actual time it takes for the burst release to occur (burst time).

2. Materials and methods

2.1. Materials

Rivastigmine hydrogen tartrate was supplied by Novartis (Basel, Switzerland). The excipients used for the preparation of the formulations of both the inner and outer tablets and also for the coating formulation of the inner tablet were purchased from different suppliers as follows: food grades of low methoxyl pectin and calcium pectinate (CaP) powder, containing 4% calcium, from Copenhagen Pectin Kelco (GA, USA), ethylcellulose NF (EC), with different viscosity grades (EC7 and EC20), from Dow Chemical Company (MI, USA), Microcrystalline cellulose (Avicel PH 101) (MCC) from FMC corporation (PA, USA), polyvinylpyrrolidone K-90 and K-30, (PVP K-90 and PVP K-30) (USP grade), and cross polyvinylpyrrolidone, (USP grade) (Crospovidone, CPVP), from BASF (Ludwigshafen, Germany), magnesium stearate (USP grade) from Merck (Darmstadt, Germany) and silicone dioxide (Aerosil 200) from Evonik-Degussa GmbH (Essen, Germany).

Table 1
The composition of the inner core containing 4.8 mg rivastigmine tartrate.

Components	mg	%	Function
Rivastigmine granulate < 420 mic	34.3	49.0	
MCC	28.6	40.8	Filler/Hardness enhancer
PVP K90	0.9	1.3	Binder
Rivastigmine tartrate	4.8	6.9	The active material
CaP granulate < 420 mic	27.3	39.0	
CaP	24.8	35.5	Water absorbing agent
EC7	1.0	1.4	Binder
CPVP	1.5	2.1	Intra disintegrant
CPVP	7.0	10.0	Inter disintegrant
Aerosil 200	0.7	1.0	Glidant
Mg stearate	0.7	1.0	Lubricant
Total	70	100	

2.2. Methods

2.2.1. Preparation of the inner tablet

The formulation of the inner tablet is presented in Table 1. A wet granulation method was used to prepare the blend for the compression in the tablet press. CaP powder was granulated in order to improve its flowability and compressibility. The granulated CaP also swells more efficiently than the CaP powder, allowing the lowering of the concentration of CaP in the formulation. For this purpose, the solution of a low viscosity ethylcellulose (EC7) (1.6 g) in ethanol (10 ml) was slowly added onto a mixture of CaP powder (40 g) and CPVP (2.4 g) while mixing with a mortar and pestle. The resulting mixture was then dried at 40 °C for about 16 h, which eventually yielded a water content of 3% as measured by a loss on drying method. Thereafter, the dried CaP granulate was milled and sieved through a 420 μ sieve using a Haver EML 200 digital T sieve shaker (HAVER & BOECKER, Oelde, Germany).

The granulation of rivastigmine tartrate was performed using a solution of rivastigmine tartrate (8.5 g which was carefully weighed directly into a beaker) and PVP K90 (1.6 g) in purified water (20 g). The solution was then slowly added onto MCC (50 g) while mixing with a mortar and pestle. The residues of the solution left in the beaker were rinsed with additional volume of purified water (5 ml) and also added onto the granules. The wet granules were then dried at 85 °C for 12 h which yielded a water content of 2.1%. The dried granules were finally milled and sieved through a 420 μ sieve.

Next, the rivastigmine tartrate granules were mixed with silicone dioxide (Aerosil® 200) (1.4 g) for 5 min to improve its flowability. The mixture was then transferred to a polyethylene bag and mixed with CPVP (14 g) and granulated CaP (54.6 g) for 20–30 min. Magnesium stearate (1.4 g) was added and mixed for an additional 2–3 min.

Biconvex 5 mm cores were compressed automatically using a Korsch EK-0 (Korsch AG, Berlin, Germany) single punch tablet press operated by an Erweka drive unit (AR 400) (ERWEKA GmbH, Heusenstamm, Germany). The cores weighed, on average, 70 mg (of 10 cores, with an RSD, relative standard deviation, of 0.5%) and presented a mean hardness of 10 Kp (RSD = 2.8%).

2.2.2. Coating process of the inner tablet

The coating process was performed using a unique combination formulation of ethylcellulose and CaP as detailed elsewhere [21].

Table 2
The composition of the outer tablet containing 4.8 mg rivastigmine tartrate.

Components	mg	%	Function
Rivastigmine granulate < 250 mic	82.8	34.5	
Lactose	54.0	22.5	Filler
Starch	23.3	9.7	Diluent/Disintegrant
PVP K90	0.7	0.3	Binder
Rivastigmine tartrate	4.8	2.0	The active material
Pectin	120.0	50.0	Release controlling agent
Microcrystalline cellulose	24.0	10.0	Filler/Hardness enhancer
PVP K30	12.0	5.0	Binder
Mg stearate	1.2	0.5	Lubricant
Total	240	100	

Briefly, the coating suspension was prepared by dissolving ethylcellulose EC20 (8 g) in ethanol (200 g) and then suspending CaP powder of particle size < 150 μ (12 g) into the solution, to receive a weight ratio of 2:3 of EC:CaP. The coating suspension was kept vigorously stirred throughout the coating process to prevent calcium pectinate precipitation. The tablets were then coated with this suspension to a desired weight gain (the incremental weight upon the coating) for each tablet.

The coating process was carried out in a laboratory perforated pan coater, equipped with a peristaltic pump (Masterfiex, Digital Console Drive, Cole-Palmer Instrument Company, IL USA) and a spraying nozzle with a tip orifice of 1.2 mm. The coating conditions such as spray rate, adjusted to 3 ml/min, the tablet temperature, set at 26°C-30 °C, the air flow rate through the coater chamber, regulated in the range of 2.75–2.85 m/s, and the rotation speed of the pan were kept constant throughout the coating process.

2.2.3. Preparation of the outer tablet

Table 2 presents the formulation of the outer tablet. First rivastigmine tartrate (4.1 g), which was carefully weighed directly into a beaker, and PVP K90 (0.7 g) were completely dissolved in purified water (10 ml). The resulting solution was slowly added onto a mixture of lactose (45.6 g) and starch (19.6 g) while mixing with a mortar and pestle. The residues of the solution left in the beaker were rinsed with an additional volume of purified water (5 ml) and added onto the granules.

The wet granules were then dried at 85 °C for 12 h which yielded a water content of 2.5%. The dried granules were finally milled and sieved through a 250 μ sieve.

Next, the rivastigmine granulates so obtained (128.5 g) were mixed with low methoxy pectin (186.5 g), microcrystalline cellulose (37.3 g) and PVP K30 (18.65 g) for 20–30 min in a polyethylene bag. Magnesium stearate (1.86 g) was added and mixed for an additional 2 min. The resulting mixture was then compressed around the inner coated tablet using a rotary tablet press-coater machine (F12415D - KILIAN RUD PRESSCOATER, Romaco- Kilian, Berlin, Germany) to obtain a tablet-in-tablet with a total diameter of 9 mm. The incremental weight contributed by the outer tablet was 240 mg where the inner and the outer tablet each contained 3 mg rivastigmine corresponding to 4.8 mg rivastigmine tartrate.

2.2.4. In-vitro dissolution release of the drug

The in-vitro release patterns of the formulations of the final tablet-in-tablet and the inner tablet before the compression coating were examined by the USP dissolution paddle method, apparatus type II, at 50 rpm using a VK 7000 dissolution tester (Vankel Technology Group Inc. NC, USA) as described previously [21]. The tablets were placed in the standard dissolution vessels (1 tablet in each vessel - in a total 6 vessels) containing 900 ml of dissolution medium, which was maintained at the temperature of 37 °C ± 0.5 °C by a VK650A heater/circulator device (Vankel Technology Group Inc. NC, USA). For testing the release rate of the drug from the outer tablet, first the dual tablets were placed in a simulated gastric fluid (0.1 N HCl, pH 1.2) for 1 h and then the dissolution medium was changed to a simulated intestinal test solution (phosphate buffer, pH 7.5, without enzymes). The inner tablets, on the other hand, were directly tested in the simulated intestinal test solution (phosphate buffer, pH 7.5, without enzymes). Samples of 3 ml were taken at different intervals up to 10 h using a VK 8000 autosampler (Vankel Technology Group Inc. NC, USA). Immediately after sampling, an equivalent volume of the dissolution media was added into the vessels in order to maintain the constant volume (sink condition).

The samples were analyzed by an isocratic HPLC method using an Agilent 1200 (G1315C) (Agilent Technologies, CA, USA) equipped with a diode-array UV detector. The chromatographic separation was achieved by a reversed phase C18 column, Kinetex® 5 μm, 100 Å, LC Column 250 × 4.6 mm Ea (Phenomenex, California, USA) maintained at 27 °C. The mobile phase was prepared by mixing a phosphate buffer (adjusted to pH = 3 ± 0.1 using an ortho phosphoric acid) and acetonitrile in the ratio of 70:30% v/v. The mobile phase was filtered, through a 0.45 μm nylon membrane, and degassed prior to use. The samples taken from the dissolution cells were first filtered through a 0.45 μm syringe filter prior to the injection into the HPLC system. The injection volume was fixed at 20 μl and the isocratic flow rate was 1.0 ml/min. The detection of rivastigmine was monitored at an UV wavelength of 217 nm.

The method was validated according to the International Conference on Harmonization (ICH) guidelines [22] and the United States Pharmacopeia and National Formulary (USP 37-NF 32) [23].

3. Results and discussion

Generally, the delivery system was planned to provide two consecutive pulses of rivastigmine release where a break of 6–6.5 h had to exist between the peaks of the first and the second pulse. Note that the peak of a pulse is defined as the time point (t_{max}) at which a maximum concentration of rivastigmine (c_{max}) is achieved in the dissolution medium.

The outer tablet was designed to provide the first pulse whereas the inner tablet in turn had to release the second pulse. The inner tablet was a film-coated tablet using a unique coating formulation which was designated to delay the second pulse for a certain period of time (lag time) after the first pulse has been already ended. In this way a break between two pulses could be created. Under these circumstances, it was, therefore, very important to carefully design the delivery system in order to achieve a precise time-controlled release of rivastigmine. Particularly, the lag time, which is provided by the coating of the inner tablet, had to be carefully controlled by, for instance, the coating weight in order to create the needed gap between two pulses. Likewise, as a primary requirement, the release profile of the drug from the outer tablet was planned to be as an immediate release, being sustained for up to 4 h. The inner tablet, on the other hand, was especially designed to release the drug in a burst manner immediately after the breach of the inner film-coating.

The following are the results of the dissolution test performed on the designed dual tablet (tablet-in-tablet) as well as on the inner tablet as is, before the compression-coating process. The latter was especially important in order to explore how the lag time, created by the coating system of the inner tablet, could be affected by the coating weight and also by the compression force during the compression-coating process. Six different tablets were tested by the dissolution test and the rivastigmine release versus time was recorded.

3.1. The release profile from the outer tablet

The results of the release rate of rivastigmine tartrate from the formulation of the outer tablet, presented as the cumulative percentage

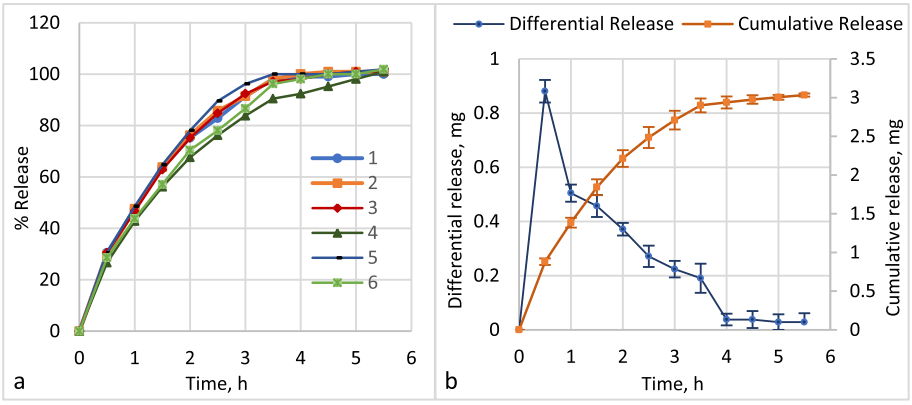

Fig. 2. The release rate of rivastigmine from the outer tablet presented by (a) cumulative percentage of release from six tablets and (b) the average cumulative amount of release and the average differential release (the dissolution test was performed first in 0.1 N HCl solution for 1 h which was then changed to simulated intestinal test solution of phosphate buffer, pH 7.5, without enzymes).

of release versus time, are shown in Fig. 2a. The average cumulative amount of the drug (expressed by mg of the drug) released from the outer tablets versus time is shown in Fig. 2b. Likewise, in order to accentuate the pulse nature of the release and also to signify the time at which the pulse reaches maximum (t_{max}), the average incremental amount of the drug (the differential release), added over time from the outer tablet into the dissolution medium, is also plotted in Fig. 2b. Note that this incremental amount was calculated by the subtraction of the concentration of rivastigmine measured in the dissolution medium at a certain time point from the concentration measured at the previous time point.

As can be seen for this formulation, one can absolutely obtain the desired short sustained release pattern of the first pulse taking place over 3.5–5 h (Fig. 2a). A release of 90% was obtained between 2.5 and 3.5 h for the fastest and the slowest tablets respectively among the six different tested tablets.

According to the average cumulative amount of drug release and the average differential release demonstrated in Fig. 2b, one can notice that whereas the release lasts over 4 h, the t_{max} of this pulse of release appeared at 30 min. This finding indicates that this specific formulation, designed for the outer tablet, combines the nature of both immediate release and sustained release formulations, in order to impart a relatively long-lasting effect, reduce side effects and to eliminate the possibility of tolerance development.

3.2. The release profile from the inner tablet before compression-coating

The inner tablet applied in this research was especially designed to provide an accurate time-controlled delivery of the second pulse of the rivastigmine release. The mechanism of the time-controlled delivery of the drug from this tablet is associated with the unique nature of the combination of a fast disintegrating core and a specific water insoluble coating. The film-coating, controlling the water diffusion rate into the core, provides a predetermined lag time which can be controlled by different parameters such as the weight ratio between the film forming polymer and water insoluble hydrophilic particulates and also the coating weight (corresponding to the thickness of the film coating) [21]. Likewise, since the mechanism of action of such a time-controlled delivery system is based on the evolvement of an osmotic pressure in the core over time, additional parameters such as the weight and the diameter of the core may also influence the lag time. In order to exactly adjust the coating weight to the needed lag time, a specific experiment was carried out where the inner cores with varying coating weights were taken during the coating process for the dissolution test (6 tablets for each coating weight) to determine the correlation between the coating weigh and the lag time. The resulting correlation from this series of the experiment is illustrated by Fig. 3. As one can realize, the correlation between the resulting lag time and the coating weight presents an exponential behavior. This behavior indicates a high

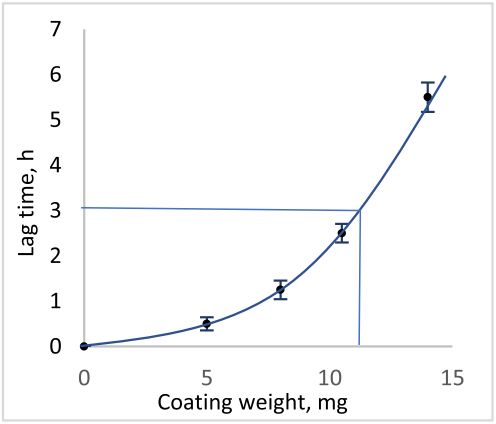

Fig. 3. The correlation between the film-coating weight of the inner tablet and the lag time for a coating combination based on CaP:EC with a weight ratio of 3:2 (the dissolution test was performed in simulated intestinal test solution of phosphate buffer, pH 7.5, without enzymes).

sensitivity of the lag time to the coating weight where a slight increase in the coating weight may lead to a significant increase in the lag time, especially in the larger coating weights (Fig. 3). This feature can be elucidated by the fact that cores with small diameters, such as 5 mm (the diameter of the inner tablet), have essentially a lower ratio of the core mass to the surface area. Therefore, at a certain coating weight (coating thickness), the film coat may exert a substantial resisting force against the osmotic pressure being developed inside the core, hindering the burst release. Consequently, a significantly longer time is needed to create the osmotic pressure which is able to overcome the coating film strength.

Based on these results, a coating weight of about 11 mg, resulting in a 3-h lag time (Fig. 3), was further used for coating the inner core.

The release pattern of the inner tablet's samples (six coated tablets), before undergoing compression coating, is illustrated by Fig. 4a. As one can see, the applied coating combination provided a lag time ranging between 3 and 3.5 h. According to Fig. 4b, presenting the average differential release and the average cumulative amount of the drug released from these tablets, one can detect that the tablet does reveal the nature of a burst release where about 1.3 mg of rivastigmine (corresponding to about 43% of the initial content of the drug in the tablet) was released during the first 30 min upon the breach of the film coat. The peak of the pulse appeared at a time point of 3.5 h, immediately after the coating film was breached.

The high disparity in the release rate between the tablets, which is represented by the high values of standard deviation and especially recognized by the average differential release presented in Fig. 4b, is the result of the difference in the lag time between the coated tablets causing a significant gap in the release level, especially immediately

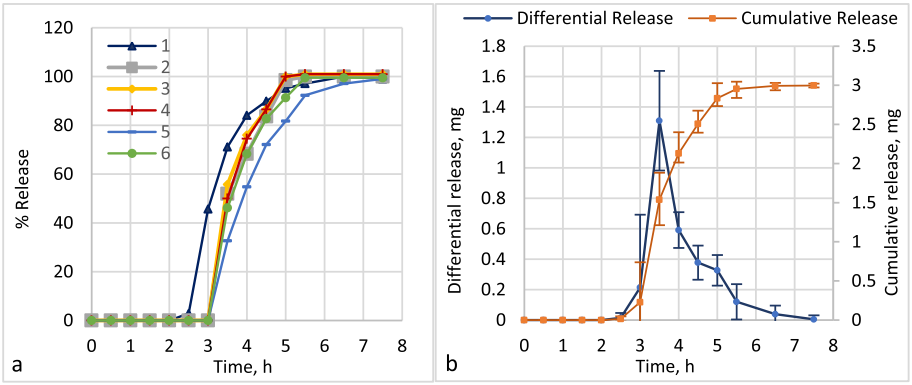

Fig. 4. The release profile of rivastigmine from the inner tablet before the compression-coating presented by (a) cumulative percentage of release from six tablets and (b) the average cumulative amount of release and the average differential release (the dissolution test was performed in simulated intestinal test solution of phosphate buffer, pH 7.5, without enzymes).

after the breach of the film coat occurs. Note that the difference in the lag time is attributed to the slight difference in the coating weight between the tablets which may especially be expressed due to the small diameter of the inner tablet as discussed above.

3.3. The release profile from the inner tablet after compression-coating

In order to explore the impact of the compression-coating on the inner tablet performance, a placebo formulation identical to that of the outer tablet was compressed onto the inner tablets. The placebo formulation was exactly the same as prepared for the active formulation but rivastigmine was equally replaced by lactose and starch.

The corresponding dissolution results for the inner tablets after the compression-coating are given in Fig. 5a and b. Fig. 5a presents the cumulative percentage of release from six different tablets whereas Fig. 5b demonstrates the average differential release and the average cumulative amount of the drug released from these tablets. As can be noticed, the lag time has been extended to about 6 h as compared to the inner tablets before the compression-coating (Fig. 4a and b). However, given the fact that the time it takes for the outer tablet to disintegrate is about 3 h (Fig. 2a and b), one can conclude that such an extension in the lag time is a direct effect of the coverage made by the outer tablet surrounding the inner tablet, which hinders, at least partially, the penetration of water into the inner core. It is noteworthy that based on the time-controlling mechanism of the inner tablet, the osmotic pressure evolvement is initiated, by the intake of the aqueous solution into the inner core, solely after the tablet is exposed to the solution.

The extension in the lag time, caused by the outer tablet, is the consequence of the fact that the disintegration of the outer tablet is accompanied by the formation of a diffusion boundary layer, which is initiated by the exposure to the aqueous liquid, to form a gentle hydrogel layer. Principally, at the first stage of the exposure, the surface of the tablet is wetted and pectin, which is capable of a gel formation, hydrates to form a hydrogel layer around the matrix. Such a hydrogel layer further, in turn, controls the permeation of the liquid to the lower layers of the outer tablet. The inner tablet remains essentially dry at this stage, which may last about 3 h creating the extra delay time in the release.

One additional point that arises from this part of the study is the fact that the lag time created by the time-controlling film-coating combination of the inner tablet (Fig. 3a and b) did not change upon the compression-coating process. This point indicates that the compression force exerted on the inner tablet did not cause any damage to the film-coating combination of the inner tablet. One of the biggest concerns, considered during the study, was that ethyl cellulose as a non-flexible polymer, which was used as the film forming component in the inner film-coating formulation, may crack during the compression coating, leaving pathways for the solution's penetration into the core, thus causing a shortened lag time. Principally, the selection of the components for the outer tablet formulation was based on the basic requirements, including proper mechanical properties (such as hardness), drug release characteristics, stability (non-friability), and processing. Additionally, the capability of the formulation to absorb the compression-associated stress was also taken into consideration. The specific combination of lactose, starch, microcrystalline cellulose and pectin, which are also known as stress-absorbing agents [24], could create the right formulation for the outer tablet which complied with all requirements mentioned above, while still cushioning the inner tablet against the compression force.

In terms of the drug release profile, the burst release nature of the second pulse remained almost unchanged after the compression process as can be seen in Fig. 5a and b. On the average about 60% of the drug was released within 1 h upon the onset of release.

3.4. Double pulse release of rivastigmine

The release profile of the dual delivery system (tablet-in- tablet) containing 6 mg rivastigmine in total (3 mg in each of the outer and inner tablet), is shown in Fig. 6. The release profile presented in this figure was the average of 6 different tablets. Accordingly, based on both

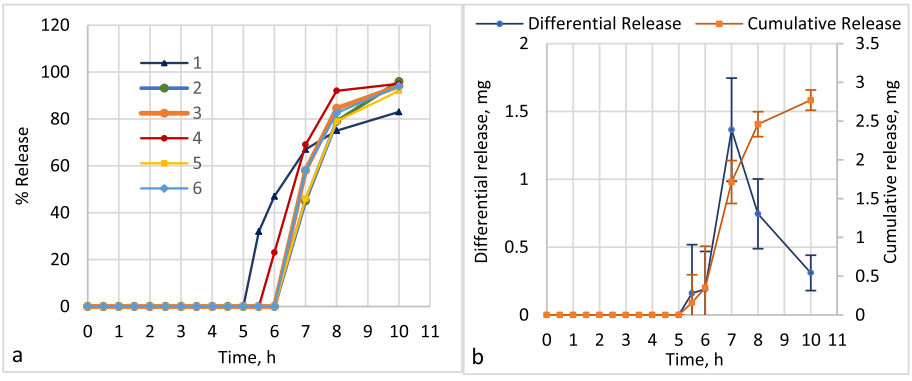

Fig. 5. The release profile of rivastigmine from the inner tablet after the compression-coating presented by (a) cumulative percentage of release from six tablets and (b) the average cumulative amount of release and the average differential release (the dissolution test was performed in simulated intestinal test solution of phosphate buffer, pH 7.5, without enzymes).

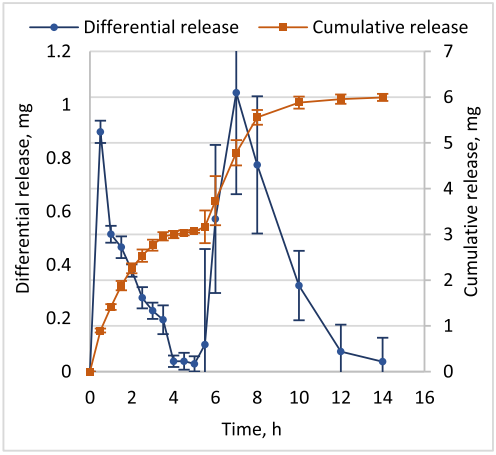

Fig. 6. The release profile of rivastigmine from a dual tablet (tablet-in-tablet) presented by the average cumulative amount of release and the average differential release (the dissolution test was performed first in 0.1 N HCl solution for 1 h which was then changed to simulated intestinal test solution of phosphate buffer, pH 7.5, without enzymes).

differential and cumulative release profiles, the designed delivery system provides two separate pulses which are associated with the outer and inner tablets respectively. Based on the differential release, whereas the peak of the first pulse appeared after 0.5 h, the second peak reaches after 7 h leaving a gap of 6.5 h between the two peaks. The break in the drug release between the two pulses, which is attributed to the water-insoluble coating combination of the inner tablet providing a time-controlled delayed release, was about 1.5 h (lag time of 2 h) where the onset of the release from the inner tablet occurs at time point of 6 h. Considering the fact that the lag time of the coated inner tablet before the compression coating was about 3 h (Fig. 4), it can be concluded that the coverage of the inner tablet by the outer tablet could provide an additional 3-h delay. On the other hand, since the release from the outer tablet lasted 4 h, one can figure out that the inner tablet starts absorbing the liquid about 1 h before the release from the outer tablet has ended where approximately 92% (about 2.8 mg) of the rivastigmine content in the outer tablet has already been released.

It is noteworthy that the total release of rivastigmine from this dual delivery system lasted over more than 10 h indicating that a long lasting therapeutic effect may be provided, for the first time, via a non-typical extended release formulation.

4. Conclusion

The currently available rivastigmine oral formulations suffer from several shortcomings, such as poor patient compliance and severe adverse effects. The two-pulse delivery system, as designed in the present study, may be an alternative method for the oral administration of rivastigmine. The specific release profile of each pulse provides a once daily formulation where rivastigmine is released in two separate doses over 10 h with a break of 1.5 h between the end of the first dose and the beginning of the second dose. The fact that the currently marketed rivastigmine formulations require a titration process indicates that the drug might develop tolerance in a prolonged administration, which requires increasing either the dose level or dose frequency. As such, the pulsatile release of rivastigmine can be a preferred method to avoid such a situation.

However, despite the fact that the selected preparation method used in this study is a novel technology and offers many advantages, such as ease and speed of the production process, still great attention must be addressed to the coating process of the inner tablet. As shown in this study, due to the small diameter of the inner tablet (5 mm), a slight excess in the coating weight may lead to a significant increase in the lag time so that the tolerance of the thickness may be very limited. Therefore, during the coating process of the inner tablet an accurate coating weight must be applied in order to obtain the exact lag time, which is the key of success for the precise performance of such a time-controlled delivery system. Additionally, a clinical trial should be performed to determine the in-vitro-in-vivo correlation especially of the inner tablet, to adjust the exact lag time associated with the weight of the inner film-coating combination.

Conflicts of interest

The authors declare that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Dedication

This study is dedicated to the memory of Penhas Penhasi.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jddst.2018.08.009.

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